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EXAMINER	
DUNSTON, JENNIFER ANN	
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1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/661,242	LIEW ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-33,37-40,42-44,46-48 and 50-70* is/are pending in the application.

4a) Of the above claim(s) *29-33,53-61,65 and 67-70* is/are withdrawn from consideration.

5)☒ Claim(s) *37* is/are allowed.

6)☒ Claim(s) *37-40,42-44,46-48,50-52,62-64 and 66* is/are rejected.

7)☒ Claim(s) *40* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 1/26/2007, in which claims 1-28, 34-36, 41, 45 and 49 were canceled; claims 29-33, 37-40, 42-44, 46-48 and 50-61 were amended; and claims 62-70 were newly added. Currently, claims 29-33, 37-40, 42-44, 46-48 and 50-70 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Election/Restrictions

Applicant elected Group II and TNFAIP6 and TGFB1 as the combination of biomarkers with traverse in the reply filed on 3/29/2006.

Claims 29-33, 53-61, 65 and 67-70 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. It is noted that new claims 65 and 67-70 do not read on the combination of elected markers: TNFAIP6 and TGFB1. As stated in the reply filed 3/29/2006, "TNFAIP6 is found in Figure 7A, line 921, and Figure 6C, line 135, while TGFB1 is found in Figure 6B, line 18, and Figure 7A, line 1120." See page 12, paragraph 4. Claims 65 and 67-70 do not read on the elected combination of genes, as the recited Figures do not contain both of the elected genes. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/29/2006.

This application contains claims 29-33 and 53-61 drawn to an invention nonelected with traverse in the reply filed 3/29/2006. A complete reply to the final rejection must include

cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Currently, claims 37-40, 42-44, 46-48, 50-52, 62-64 and 66 are under consideration.

Priority

A nonprovisional application claiming the benefit of a provisional application is not required to be copending with the provisional application. Abandonment of a provisional application for failure to pay the basic filing fee would indicate that the nonprovisional application could not claim the benefit of the provisional application because the basic filing fee was not paid within the time period set forth in 37 CFR 1.53(g) as required by 37 CFR 1.78(a)(4).

In the instant case, provisional application number 60/410,180 was not abandoned for failure to pay the basic filing fee.

Specification

It is suggested that the figures, which contain text concerning the differential expression of genes in osteoarthritis, be incorporated as TABLES into the specification. As figures, this data is not text searchable in the US patent databases. Putting the information into text-based tables would make the information more search-accessible to the public in the event this application issues as a patent.

It is noted that the reply filed 1/26/2007 indicates that Applicant will consider incorporating as TABLES into the specification text concerning the differential expression of genes in OA, upon the indication of allowable claims.

Claim Objections

Claim 64 is objected to because of the following informalities: the term "RT-PCR" is misspelled. Appropriate correction is required. This is a new objection, necessitated by the addition of new claim 64 in the reply filed 1/26/2007.

Response to Arguments - Claim Objections

The objection of claims 34-36 is moot in view of Applicant's cancellation of the claims in the reply filed 1/26/2007.

Response to Arguments - Double Patenting

The provisional rejection of claims 35, 36, 38, 42, 46 and 50 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13, 21 and 25 of copending Application No. 10/809,67 has been withdrawn in view of Applicant's amendment to the claims in the reply filed 1/26/2007.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 62 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection, necessitated by the addition of new claim 62 in the reply filed 1/26/2007.

Claim 62 is vague and indefinite in that the metes and bounds of the phrase "wherein a cDNA or EST complementary to said RNA encoded by said gene is immobilized to a microarray" are unclear. It is unclear how the immobilized cDNA or EST complementary to said RNA relates to the method steps of claims 37, 38, 42, 46 and 50. It would be remedial to amend the claim language to clearly indicate that the step of determining is effected by hybridization of said RNA to an immobilized cDNA or EST complementary to said RNA.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38-39, 42-44, 46-48, 50-52, 62-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing mild osteoarthritis in a human test individual, said method comprising (a) for each gene of a set of genes consisting of TNFAIP6 and TGFBI, determining a level of expression of RNA encoded by said gene in a cartilage sample of a test individual, (b) for each gene of said set of genes, comparing the level of expression of said RNA in said sample of said test individual with a level of expression of RNA encoded by said gene in control cartilage samples obtained from each of the following populations: (i) human individuals not having osteoarthritis, (ii) human individuals

having mild osteoarthritis, (iii) human individuals having moderate osteoarthritis, human individuals having marked osteoarthritis, and (iv) human individuals having marked osteoarthritis, and (v) human individuals having severe osteoarthritis, does not reasonably provide enablement for a method of diagnosing any stage of osteoarthritis using any other set of genes or a method of diagnosing moderate, marked or severe osteoarthritis by determining the level of TNFAIP6 and TGFBI expression. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: Claims 38-39 are specifically drawn to a method of diagnosing mild osteoarthritis in an individual. Claims 46-48 are specifically drawn to a method of diagnosing moderate osteoarthritis in an individual. Claims 50-52 are specifically drawn to a method of diagnosing marked osteoarthritis in an individual. Claims 42-44 are specifically drawn to a method of diagnosing severe osteoarthritis in an individual.

With respect to the choice of gene, claims 38, 42, 46, 49 and 62-64 encompass the use of any gene. Claims 39, 43, 47 and 51 limit the set of genes to those genes recited in Figures 1-7. Claim 66 limits the set of genes to any set selected from Figure 7a. Claims 44, 48 and 52 limit the set of genes to TNFAIP6 and TGFBI. To diagnose the individual with either mild, moderate,

marked or severe osteoarthritis, the expression of the set of genes in a human test individual is compared to the expression of the set of genes in control samples, where said control samples are obtained from the following population of individuals (i) a population of human individuals not having osteoarthritis, (ii) a population of human individuals having mild osteoarthritis according to the Marshall scoring system, (iii) a population of human individuals having moderate osteoarthritis according to the Marshall scoring system, (iv) a population of human individuals having marked osteoarthritis according to the Marshall scoring system, and (v) a population of individuals having severe osteoarthritis according to the Marshall scoring system. The claims read on the comparison of one test human to one human selected from each of the five recited populations. The claims require that the control cartilage samples be obtained from each population, but do not require the control samples to be representative of a population.

Claim 62 requires a cDNA or EST complementary to the RNA encoded by the set of genes to be immobilized to a microarray. Claims 63 and 64 further limit the step of determining to hybridization of the RNA to a microarray, and real time RT-PCR, respectively.

The nature of the invention is complex in that the expression of the biomarkers recited in the claims must be able to distinguish between mild, moderate, marked and severe osteoarthritis when gene expression is compared between the test individual and each of the control populations. The practice of the claimed invention for the diagnosis or staging of osteoarthritis requires the knowledge of gene(s) that are differentially expressed between "normal", mild osteoarthritis, moderate osteoarthritis, marked osteoarthritis, and severe osteoarthritis. Furthermore, the alterations in gene expression between the different classes must be consistent enough within each class and between each class such that a diagnostic test of sufficient

specificity and sensitivity can be performed. In other words, the gene expression patterns tested in the claimed methods must allow one to draw a reliable conclusion regarding the presence/absence of osteoarthritis and the severity of osteoarthritis.

Breadth of the claims: The claims are very broad in that they encompass the use of the level of RNA expression of any set of genes (i.e., more than two genes) as a diagnostic of mild, moderate, marked or severe osteoarthritis. The language used to define the detected RNA is broad in nature with regard to the selection of genes from Figures 1-7. The claims encompass the detection of variants (e.g., splice variants) of the recited genes. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification teaches that "diagnosis" refers to a process of determining if an individual is afflicted with a disease or ailment (page 14, lines 27-28). The specification does not provide a single working example where the claimed method is actually practiced for the diagnosis or staging of OA in a patient, human or otherwise. The specification provides an experimental section with "examples," but these are not examples of the instantly claimed method being used.

The specification asserts that Figures 1-7 contain lists of stage-specific genes, whose level of expression is indicative of the existence of some degree of mild, moderate, marked or severe osteoarthritis when compared with the level of expression of the same one or more genes in a normal individual (e.g. page 36, lines 18-22; page 85, lines 14-22).

The examples of the specification teach the isolation of RNA from normal human cartilage and cartilage samples from areas of mild, moderate, marked or severe cartilage degeneration obtained during either arthroscopic knee surgery or total knee replacement (e.g.

pages 91-92). The specification teaches that the RNA was made into a cDNA library, from which cDNA clones (ESTs) were obtained and sequenced (e.g. page 92). The specification does not teach the number of individuals from which each cDNA library was made. The EST sequences obtained from this analysis were used to make a microarray of genes expressed in normal and diseased articular cartilage. This array appears to be referred to as the ChondroChip array in the remainder of the specification.

The examples of the specification teach that RNA samples isolated from normal or OA articular cartilage can be labeled and hybridized to the ChondroChip or Affymetrix U133A Array (e.g. pages 94-96).

Example 5 asserts that biomarkers (nucleic acids) specific for mild OA or severe OA were detected utilizing the ChondroChip. The specification states that sample RNA from either normal, mild or severe OA cartilage was labeled and hybridized to the ChondroChip with subsequent analysis identifying differences in gene expression greater than 2-fold when compared to either the intensity from the normal cartilage or any other stage specific cartilage (page 97). The specification does not teach the number of individuals analyzed for each sample class. It is unclear whether a single sample was used for each class, multiple samples were pooled for each class, or multiple samples were individually tested for each class. The nature of the comparisons is wholly unclear. For example, the specification does not teach whether each class of OA was directly compared to normal cartilage in the hybridization assay. The specification asserts that Figures 1-4 provide those genes identified as unique to either mild or severe OA. Thus, tables 1-4 do not provide any information with regard to moderate or marked osteoarthritis. Because moderate and marked OA samples were not included in this study, it is

impossible to determine whether genes that differentiate between mild and severe OA will also differentiate between mild, moderate, marked and severe OA.

Example 6 asserts that biomarkers specific for mild OA, marked OA, moderate OA and severe OA were determined. The specification teaches the hybridization of samples of RNA from normal, mild OA, moderate OA, marked OA and severe OA to the ChondroChip and Affymetrix U133A Array. The specification states that the following pairwise comparisons were made: mild/normal, moderate/normal, marked/normal and severe/normal. Using statistical tests and a p-value cutoff of 0.05, genes "associated" with OA were identified and are presented in Figures 6 and 7. These genes appear to be genes up- or down-regulated in OA, which are not affected by age, gender, hybridization date, and slide batch. This suggests that multiple samples were tested on multiple days; however, the specifics are not provided in the instant specification.

The specification characterizes the figures of the instant specification in the following manner:

Figure 1: ESTs down-regulated in cartilage isolated from patients having mild osteoarthritis, but which are not down-regulated in patients having severe osteoarthritis, when compared with cartilage isolated from normal individuals.

Figure 2: ESTs down-regulated in cartilage from patients having severe osteoarthritis, but which are not down-regulated in patients having mild osteoarthritis, when compared with cartilage isolated from normal individuals.

Figure 3: ESTs up-regulated in cartilage isolated from patients having mild osteoarthritis, but which are not up-regulated in patients having severe osteoarthritis, when compared with cartilage isolated from normal individuals.

Figure 4: ESTs up-regulated in cartilage from patients having severe osteoarthritis, but which are not up-regulated in patients having mild osteoarthritis, when compared with cartilage isolated from normal individuals.

Figure 5: ESTs up regulated in patients having mild osteoarthritis when compared to cartilage isolated from normal individuals.

Figure 6: ESTs which have been identified as being OA stage-specific markers for (a) mild OA only, (b) moderate OA only, (c) marked OA only, and (d) severe OA only in OA ChondroChip microarray analysis.

Figure 7: ESTs which have been identified as being OA stage-specific markers for (a) mild OA only, and (b) severe OA only in OA cartilage as compared to cartilage isolated from normal individuals, when the Affymetrix U133A Array is used for the analysis.

Figures 1-5 do not provide any information regarding the status of the genes or biomarkers in moderate or marked OA. Accordingly, one cannot definitively classify the stage of OA in a test individual as being mild, moderate, marked or severe based upon the data presented in Figures 1-5.

While the specification asserts that Figures 6 and 7 present data for biomarkers that are specific to one stage of OA only, the same biomarker can be found in more than one category. For example, TGFB1 is found in Figure 6b (moderate OA only, pp. 61 and 62) and Figure 7a (mild OA only, p. 753), and TNFAIP6 is found in Figure 6c (marked OA only, p. 238) and Figure 7a (mild OA only, pp. 683 and 698). Therefore, the genes listed in tables 6(a-d) and 7(a-b) are not specific to one class of OA. If one were to test an individual for the expression of TGFB1 and TNFAIP6 in articular cartilage and compare that result to an individual diagnosed

with any class of OA, one would not be able to determine if the test individual has marked OA or mild OA). Furthermore, the specification does not teach the direction of expression. Perhaps, TNFAIP6 is up regulated in marked OA and down regulated in mild OA. However, the specification does not specifically teach the direction of gene expression relative to the normal control.

The specification does not teach the actual diagnosis of any individual using the claimed method. Further, the specification does not teach the specificity or sensitivity of a diagnostic test using any combination of biomarkers, including the combination of TNFAIP6 and TGFB1.

Predictability and state of the art: The prior art teaches that there are many factors that need to be considered in order to develop a reliable genetic test. Shalon et al (US 2001/0051344 A1, Dec 13, 2001, cited in a prior action) teach that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant (see page 10, paragraph [0155]). Shalon et al further teach that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels (see page 10, paragraph [0156]). Shalon et al teach that the test average pattern is compared with a control average pattern on a microarray to identify test genes which show significantly, typically at least 2 fold and up to 100 fold or more, increase or decrease in gene expression level with respect to control levels for the same gene (see page 10, paragraph [0158]). Post filing art, Kroese et al (Genetics in Medicine, Vol. 6, pages. 475-480, 2004, cited in a prior action) teach genetic tests are heterogeneous in

nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods (e.g. page 476, 2nd column, last paragraph). Kroese et al teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (e.g. page 477, 1st column, 1st and 2nd full paragraph). Kroese et al teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (e.g. page 479, 2nd column, last paragraph). Additional post filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, Vol. 18, page 20, 2004, cited in a prior action) teach that it strikingly common for follow-up studies to find gene-disease associations wrong (e.g. page 2, 1st paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a complex disease there is only roughly a one-third chance that the study will reliably confirm the finding (e.g. page 2, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical method, should be included in the gene association studies (e.g. page 3, 2nd paragraph).

With regard to gene expression testing to diagnose osteoarthritis, Marshall et al (Osteoarthritis and cartilage, Vol. 13, pages 861-871, 2005, cited in a prior action) teach that the

level and direction of gene expression for a particular gene in a test sample and control may vary depending upon whether the RNA used to assess the level of expression is obtained from blood or cartilage (e.g. page 868, paragraph bridging columns). Marshall et al specifically teach that TNFAIP6 has been shown to be up regulated in pre-inflamed joints and in OA cartilage, but is down regulated in early OA blood samples (e.g. page 868, paragraph bridging columns). Further, Marshall et al teach that extensive statistical analysis of numerous training and test samples must be done to determine the specificity, sensitivity and accuracy of an OA diagnostic test based upon gene expression assays (e.g. page 865, right column, 2nd full paragraph; page 869, left column; Table V).

The use of TGFB1 in the specific diagnosis of mild, moderate, marked or severe osteoarthritis would be unpredictable. The instant specification teaches that osteophytes are not observed in mild OA but are present in moderate and severe OA (e.g. pages 3-4). Thus, osteophytes are a feature of moderate, marked and severe OA. Uchino et al (Clinical Orthopaedics and Related Research, Vol. 377, pages 119-125, 2000, cited in a prior action) teach that TGFB1 is expressed in osteophytes and in OA articular cartilage (e.g. Table 2). Thus, it would be unpredictable to use TGFB1 alone or in combination with TNFAIP6 to diagnose a specific class of OA.

Amount of experimentation necessary: Given the lack of guidance in the specification and prior art with regard to using gene expression to diagnose mild, moderate, marked or severe osteoarthritis, the quantity of experimentation in this area is very large. Due to the lack of detail provided in the specification with respect to the direction of expression of the genes in Tables 6 and 7, and lack of statistical analysis with respect to the predictive value of any combination of

genes from Tables 1-7, one would have required a large amount of experimentation to carry out the claimed invention.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 38-39, 42-44, 46-48, 50-52, 62-64 are not considered to be enabled by the instant specification.

Response to Amendment – Declaration of Hongwei Zhang, Ph.D.

The declaration under 37 CFR 1.132 filed 1/26/2007 is sufficient to overcome the rejection of claims 37 and 40 based upon insufficiency of disclosure under 35 U.S.C. 112, first paragraph. The declaration provides evidence that the expression levels of TNFAIP6 and TGFBI RNA can be used to diagnose mild osteoarthritis when expression levels of a test individual are compared with the expression levels in unaffected individuals.

The declaration under 37 CFR 1.132 filed 1/26/2007 is insufficient to overcome the rejection of claims 38-39, 42-44, 46-48, 50-52, 62-64 based upon insufficiency of disclosure as set forth in the last Office action.

The declaration provides evidence that TNFAIP6 and TGFBI RNA expression levels can be used as a diagnostic marker of mild osteoarthritis. However, this showing is not commensurate in scope with the rejected claims, and the differences between the claimed invention and the showing under 37 CFR 1.132 would not have been to one of ordinary skill in the art at the time the invention was made, due to the unpredictable nature of the invention (see

pages 15-17 of the Office action mailed 7/26/2007). The declaration does not provide evidence that genes other than the combination of TNFAIP6 and TGFBI can be used to diagnose mild osteoarthritis. Further, the declaration does not provide evidence that TNFAIP6 and TGFBI expression levels can be used to diagnose moderate, marked or severe osteoarthritis. The declaration does not provide evidence that a representative number of gene combinations encompassed by the claims can be used to diagnose mild, moderate, marked or severe osteoarthritis.

Upon consideration of the evidence as a whole, the declaration is insufficient to overcome the rejection of claims 38-39, 42-44, 46-48, 50-52, 62-64 under 35 U.S.C. 112, first paragraph.

Response to Arguments - 35 USC § 112

The rejection of claims 34-52 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of Applicant's amendment to the claims in the reply filed 1/26/2007.

The rejection of claims 34-36, 41, 45 and 49 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is moot in view of Applicant's cancellation of the claims in the reply filed 1/26/2007.

Applicant's arguments, see pages 21-25, filed 1/26/2007, with respect to the rejection of claims 37 and 40 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement have been fully considered and are persuasive. The previous rejection of claims 37 and 40 has been withdrawn.

With respect to the rejection of claims 38-39, 42-44, 46-48, 50-52, 62-64 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, Applicant's arguments filed 1/26/2007 have been fully considered but they are not persuasive.

The response essentially asserts that the specification provides sufficient guidance to allow one to practice the claimed invention with only routine experimentation to determine which gene expression patterns correlate with which disease in a statistically significant manner. As noted by Applicant, "claims are not broader than the enabling disclosure if 'a person skilled in the relevant art could determine which conceived but not-yet-fabricated embodiments would be inoperative with expenditure of no more effort than is normally required' in the art."

The response asserts that the specification provides figures that contain genes which are differentially expressed in various stages of arthritis. However, fewer than five samples were used in some of the analyses (e.g., response page 25). Testing only three or four individuals for one group may not be representative of the population being tested. As stated by Shalon et al, more samples are typically required to achieve statistical significance. Given the lack of information provided with regard to the direction of gene expression and statistical significance in the present specification, the reliability of the results is not known. One would be required to perform additional experimentation to correlate the Marshall score with the level of gene expression for a representative number of gene sets selected from the set of all human genes. While the techniques of measuring gene expression are routine in the art, the unpredictable nature of the invention (pages 15-17 of the Office action mailed 7/26/2007) means that one cannot predict the inoperability of any gene set encompassed by the claims. The association of gene expression to disease for diagnostic purposes is unpredictable. It is noted that patent

protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. In instant case, identifying sets of genes whose expression levels are diagnostic of a stage of a disease is not considered routine in the art and without sufficient guidance to a specific sets of genes whose expression levels allow one to reliably distinguish between affected and unaffected individuals as well as the different stages of disease, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

Claim 37 is allowed.

Claim 40 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

jad

CELINE QIAN, PH.D.
PRIMARY EXAMINER